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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,225	02/14/2002	Fernando Donate	38342-178463	6196

30827 7590 06/28/2006

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EXAMINER
BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,225	DONATE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-55* is/are pending in the application.

4a) Of the above claim(s) *3,4,16-48 and 50-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-15 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 April 2006 has been entered.

2. Claims 6 and 56-57 are cancelled.

Claims 1-5 and 7-55 are pending.

Claims 1-2, 8-10 and 12-13 have been amended.

Claims 3-4, 16-48 and 50-55 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 1-2, 5, 7-15 and 49 are under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The objection to claim 57 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the cancellation of the claim.

7. The rejections of claims 1-2, 7-15, 49 and 56-57 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "human HGRP" and rabbit HGRP" is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1-2, 5, 7-15, 49 and 56-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1, 5-15, 49 and 56-57 under 35 U.S.C. 102(e) as being anticipated by Olsson et al as evidenced by Koide et al and Borza et al is withdrawn in view of the amendments to the claims.

10. The rejection of claims 1-2, 11, 13 and 49 under 35 U.S.C. 102(b) as being anticipated by Borza et al (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02) as evidenced by Donate et al (Cancer Research, 64(16):5812-5817, 15 August 2004) withdrawn in view of the amendments to the claims.

11. The rejection of claims 1-2, 5, 7-15 and 49 under 35 U.S.C. 103(a) as being unpatentable over Borza et al (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02) in view of Azizkhan et al (Journal of Experimental Medicine, 152(4):931-944, 1 October 1980) and Simantov et al (US 2001/0041670 A1, 12/6/1999, cited previously on PTO-892 mailed 11/17/2004) is withdrawn in view of the amendments to the claims.

New Grounds of Objections/Rejections

12. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 15, lines 12 and 16. Applicant's cooperation is requested in reviewing the entire disclosure for additional embedded hyperlinks and/or other form of browser-executable code that require correction. See MPEP § 608.01.

b. The first line of the specification needs to be amended with a benefit claim to U.S. Provisional Application Serial No. 60/268,370, filed 02/14/2001. Applicant is reminded that the priority applications cannot be incorporated by reference after the original filing of the instant application. See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

c. At pg. 28, lines 4-5 of the specification it states "(again, I do not see the description of this for the protein and peptide)???", which appears to be misplaced. Clarification or correction is required.

d. The use of the trademarks Matrigel®, Texas Red™, DiffQuik®, X-acto®, Permount® as well as others have been noted in this application (e.g., see pg. 10, line 29, pg. 11, lines 2 and 4, pg. 26, line 5, pg. 33, lines 3, 10, 12, 21, 23 and 24, pg. 34, various lines, pg. 35, line 4, pg. 36, various lines, pp. 36-38, pg. 48, line 18). It should be capitalized wherever it appears and be accompanied by the generic terminology. As the list of pages and line numbers provided by the examiner is not intended to be a complete list, Applicant's cooperation is requested in reviewing the entire disclosure for additional trademarks that require correction.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate correction is required.

Oath/Declaration

13. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of each inventor. The citizenship of inventor Fernando Donate is missing.

14. The rejection of claims 1-2, 11, 13 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Borza et al [a] (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02).

The claims are interpreted as being drawn to an anti-angiogenic polypeptide or peptide consisting of the sequence (His/Pro)-(His/Pro)-Pro-His-Gly (SEQ ID NO:7) or an addition variant thereof having an additional 1 to 4 amino acids selected from His, Pro or Gly at the N- or C-terminus of the pentapeptide and said anti-angiogenic polypeptide or peptide and a pharmaceutically acceptable carrier in a pharmaceutical composition suitable for injection and an affinity ligand useful for binding to or isolating an HPRG-

binding molecule comprising the polypeptide or peptide of claim 1 or 2 immobilized on a solid support or carrier. For this rejection, the term "having" is being interpreted as equivalent to "comprising", which is open-ended claim language and is inclusive to unrecited elements (MPEP 2111.03).

Borza et al [a] teach the H/P domain from human and rabbit HPRG, which is being interpreted as an addition variant polypeptide or peptide of SEQ ID NO:7 consisting of SEQ ID NO:7 and having an additional 1 to 4 amino acids (His, Pro or Gly) at the N- or C-terminus of SEQ ID NO:7 in view of the transitional term "having", which is being interpreted as open claim language and as such reads upon the human and rabbit H/P domain (see entire document, particularly Figs 2-4, Table 1 and page 1927, right column). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Further, artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999). Thus, the H/P domain of human and rabbit HPRG as taught by Borza et al [a], consists of SEQ ID NO:7 and is interpreted as "having" an additional 1 to 4

amino acids selected from His, Pro or Gly at the N- or C-terminus of SEQ ID NO:7 and necessarily possesses the claimed properties/activities.

Borza et al [a] also teach the H/P domain of rabbit HPRG in 5 mM phosphate buffer, pH 7.2, which is reasonably interpreted to be a pharmaceutically acceptable carrier and in suitable form for injection (see page 1926, right column). Further, Borza et al [a] teach the H/P domain of rabbit HPRG bound to a DEAE-cellulose column (i.e., solid support), which is interpreted as an affinity ligand useful for binding to or isolating an HPRG-binding molecule (see bridging paragraph of pages 1928-1929).

Thus, Borza et al [a] anticipate the claims.

15. Claims 1-2, 5, 7-15 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borza et al [a] (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02) in view of Azizkhan et al (Journal of Experimental Medicine, 152(4):931-944, 1 October 1980, cited on PTO-892 mailed 7/7/2005) and Borza et al [b] (The Journal of Biological Chemistry, 273(10):5493-5499, 1998, Ids filed 6/6/02) and Simantov et al (US 2001/0041670 A1, 12/6/1999, cited previously on PTO-892 mailed 11/17/2004).

Claims 1-2, 11, 13 and 49 and their interpretation have been described supra. Claims 5, 7-10, 12 and 14-15 are drawn to the anti-angiogenic H/P domain polypeptide or peptide (i.e., SEQ ID NO:7 addition variant) of the human or rabbit HPRG polypeptide (SEQ ID Nos:5 or 6, respectively) that is diagnostically or therapeutically labeled, and a therapeutic anti-angiogenic pharmaceutical composition comprising said H/P domain

(i.e., SEQ ID NO:7 addition variant) of the human or rabbit HPRG polypeptide, which is bound to a therapeutically active moiety and a pharmaceutically acceptable carrier.

Borza et al [a] have been described supra. Borza et al [a] do not teach diagnostically or therapeutically labeled H/P domain of human or rabbit HPRG and a diagnostically or pharmaceutically acceptable carrier in suitable form for injection and wherein the label is selected from the labels recited in claims 8-10 and 15. These deficiencies are made up for in the teachings of Azizkhan et al and Simantov et al.

Azizkhan et al teach that heparin secreted by mast cells stimulates capillary endothelial cell migration, which is an important component of angiogenesis in vivo and the migratory activity of heparin was blocked by heparin specific antagonists (see entire document, particularly abstract).

Borza et al [b] teach that the histidine residues in the H/P domain of HPRG mediates interactions with heparin, transition metals and heme and interaction with heparin-binding proteins is largely electrostatic but requires lysine or arginine side chains in other known cases and heparin's anticoagulant effect has obvious pharmacological interest (see entire document, particularly pg. 5493, 2nd col.).

Simantov et al teach pharmaceutical compositions comprising an HPRG polypeptide and a pharmaceutically acceptable carrier (see page 3, paragraphs [0039-0040] and page 6 paragraph [0084]) and Simantov et al teach various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others (see page 10 and page 13, paragraph [0174]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domain (i.e., SEQ ID NO:7 addition variant) of HPRG taught by Borza et al [a] to detect secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domain (i.e., SEQ ID NO:7 addition variant) of HPRG to detect secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration in view of the teachings of Borza et al [a] and Azizkhan et al and Borza et al [b] and Simantov et al because Borza et al [a] teach the H/P domain of human and rabbit HPRG, which binds heparin and Azizkhan et al teach that heparin secreted by mast cells stimulates capillary endothelial cell migration, which is an important component of angiogenesis in vivo and the migratory activity of heparin was blocked by heparin specific antagonists and Borza et al [b] teach that the histidine residues in the H/P domain of HPRG mediates interactions with heparin, transition metals and heme and neutralizes heparin's anticoagulant effect, which has "obvious pharmacological interest" (Borza et al [b], pg. 5493, 2nd col.) and Simantov et al teach pharmaceutical compositions comprising an HPRG polypeptide or fragment thereof and a pharmaceutically acceptable carrier and

Simantov et al teach various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others for labeling the HPRG polypeptide or fragment thereof. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have diagnostically or therapeutically labeled the H/P domains (i.e., SEQ ID NO:7 addition variant) of Borza et al [a] with the diagnostic and therapeutic labels taught by Simantov et al to detect secreted heparin as an angiogenesis marker or to block the migratory activity of heparin and hence, angiogenesis or migration of capillary endothelial cells. Further, one of ordinary skill in the art would have been motivated to combine the diagnostically/therapeutically labeled human or rabbit H/P domain (i.e., SEQ ID NO:7 addition variant) of human or rabbit HPRG with a pharmaceutically acceptable carrier to facilitate therapeutic administration of the labeled polypeptides. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domains (i.e., SEQ ID NO:7 addition variant) of HPRG to detect secreted heparin as an angiogenesis marker and inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration in view of the teachings of Borza et al [a] and Azizkhan et al and Borza et al [b] and Simantov et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1, 5, 7-15 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borza et al [a] (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02) in view of Azizkhan et al (Journal of Experimental Medicine, 152(4):931-944, 1 October 1980, cited on PTO-892 mailed 7/7/2005) and Borza et al [b] (The Journal of Biological Chemistry, 273(10):5493-5499, 1998, Ids filed 6/6/02) and Simantov et al (US 2001/0041670 A1, 12/6/1999, cited previously on PTO-892 mailed 11/17/2004).

For this rejection, the claims are being interpreted as drawn to an anti-angiogenic polypeptide that is a conservative amino acid variant of the human HPRG H/P domain (SEQ ID NO:5) or the rabbit HPRG H/P domain (SEQ ID NO:6) having substantially the same transition metal ion, plasminogen binding activity or inhibits angiogenesis, endothelial cell proliferation, or endothelial tube formation in an *in vitro* or *in vivo* bioassay similar to the polypeptide of SEQ ID NO:5 or SEQ ID NO:6, wherein the human and rabbit H/P domain variants are diagnostically and therapeutically labeled with the recited labels and a pharmaceutical composition comprising said anti-angiogenic polypeptide variants and a pharmaceutically acceptable carrier and wherein the anti-angiogenic polypeptide is immobilized to a solid support or carrier.

Borza et al [a] teach the H/P domain from human and rabbit HPRG (i.e., SEQ ID NO:5 and 6, respectively) (see entire document, particularly Fig 2 and Table 1). Borza et al [a] do not teach conservative amino acid variants of human and rabbit HPRG or diagnostically or therapeutically labeled H/P domain of human or rabbit HPRG and a diagnostically or pharmaceutically acceptable carrier in suitable form for injection and

wherein the label is selected from the labels recited in claims 8-10 and 15. These deficiencies are made up for in the teachings of Azizkhan et al and Borza et al [b] and Simantov et al.

Azizkhan et al have been described supra.

Borza et al [b] have been described supra.

Simantov et al teach HPRG and functional variants comprising conservative amino acid substitutions as well as pharmaceutical compositions comprising the HPRG polypeptides and a pharmaceutically acceptable carrier and various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others (see pg. 3, paragraphs [0038-0040], pg. 4, 1st column, page 10 and pg. 13, paragraph [0174]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced compositions comprising diagnostically or therapeutically labeled conservative amino acid variant H/P domains of human or rabbit HPRG for detection of secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled conservative amino acid variant H/P domains of human or rabbit HPRG for detection of secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary

endothelial cells to block heparin stimulated capillary endothelial cell migration in view of the teachings of Borza et al [a] and Azizkhan et al and Borza et al [b] and Simantov et al because Borza et al [a] teach the H/P domain of human and rabbit HPRG, which binds heparin (see pages 1931 and 1933, left columns) and Azizkhan et al teach that heparin secreted by mast cells stimulates capillary endothelial cell migration, which is an important component of angiogenesis in vivo and the migratory activity of heparin was blocked by heparin specific antagonists and Borza et al [b] teach that the histidine residues in the H/P domain of HPRG mediates interactions with heparin, transition metals and heme and neutralizes heparin's anticoagulant effect, which has "obvious pharmacological interest" (Borza et al [b], pg. 5493, 2nd col.) and Simantov et al teach HPRG and functional variants comprising conservative amino acid substitutions as well as pharmaceutical compositions comprising the HPRG polypeptides and a pharmaceutically acceptable carrier and various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others and according to Borza et al [b] interaction of heparin with heparin-binding proteins is largely electrostatic but requires lysine or arginine side chains in other known cases. Therefore, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to produce conservative amino acid human and rabbit H/P domain variants, which were known to mediate heparin interaction (i.e., histidine, lysine or arginine substitutions) and there would have been an advantage to label the conservative amino acid human and rabbit H/P domain variants with the diagnostic and therapeutic labels of Simantov et al for detection of secreted heparin as

an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells. Further, one of ordinary skill in the art would have been motivated to combine the diagnostically/therapeutically labeled conservative amino acid human and rabbit H/P domain variants with a pharmaceutically acceptable carrier to facilitate therapeutic administration of the labeled polypeptides. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled conservative amino acid variant H/P domains of human or rabbit HPRG for detection of secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration in view of the teachings of Borza et al [a] and Azizkhan et al and Borza et al [b] and Simantov et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at

(571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827